The inflammatory bowel diseases require expert cooperation and interaction between gastroenterologists and surgeons. The roles of physician and surgeon are constantly changing, with increasingly valuable drug therapies available and surgery becoming more focussed and well defined. Three areas of IBD management highlight the need for optimal harmonisation between specialists.

Achieving the Balance between Drug Therapy and Surgery in IBD

The Hong Kong Society of Gastroenterology

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President Message

Welcome to our December 2014 Newsletter!

In 2014, The Hong Kong Society of Gastroenterology has seen a stable year with scientific meetings organized in March, August and November. The Society continued supporting the Medical Multispeciality Mega Conference and the IDD Forum. Apart from organizing the public education campaign on GI/GERD in May, the Society also participated in the 2014 HKU Health Exhibition. On behalf of the Society, I wish to express my gratitude to all who have contributed or supported the Society: Dr Annie OO Chan for organizing the 2014 Annual General Meeting cum Scientific Meeting, Dr Jodis TW Lam for organizing the 16th Joint Annual Scientific Meeting 2014, Professor Justin CY Wu for editing the two Newsletters this year, Professor Michael Kamm, Professor Feza Remzi, Dr Dorothy KL Chow, Dr Ivan FN Hung, Dr Leon Adams and Dr Kevin SH Liu for their contributions towards the scientific updates in this Newsletter, all fellows and members who have attended the scientific meetings and our friends from pharmaceutical industry who have sponsored our activities.

The next newsletter will be published in June 2015.

Wishing you a merry Christmas and a happy new year,

Dr. Wai-Cheung Lao
President, The Hong Kong Society of Gastroenterology

Scientific Updates

Achieving the Balance between Drug Therapy and Surgery in IBD

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Post Operative Crohn’s Disease
Eighty percent of patients will require surgery for their disease at some time in their life. Of these 70 percent will require a further operation. Every effort should therefore be made to recognise patients at increased risk of recurrence (smoking, previous surgery, and penetrating disease), optimising post operative drug therapy, and monitoring for recurrence and adjusting therapy accordingly. Most patients should receive 3 months of metronidazole. Those at higher risk should receive a thiopurine, and those at greatest risk anti-TNF therapy. Patients should have early colonoscopic assessment and treatment according to clinical risk of recurrence, therapy adjustment for early recurrence, and longer term monitoring. Faecal calprotectin appears to be suitable for monitoring, with endoscopy reserved for those with an elevated faecal inflammatory marker. Gastroenterologists and surgeons should plan joint patient care before and after surgery.
Perineal Fistulating Disease

Perineal fistulating Crohn’s disease causes great morbidity. Examination under anaesthetic and MRI are needed to characterise fistula tracks, and drainage using setons provided when necessary. Only anti-TNF therapy has been proven to heal perineal fistulating disease in the long term. Optimal anti-TNF use involves concurrent use with a thiopurine, and initial antibiotics. MRI is the optimal tool for monitoring deep healing.2-4 A range of surgical techniques have been proposed to heal fistula tracks, but most of these have not yet been demonstrated to assist in long term healing.

Severe Acute Ulcerative Colitis

Severe acute ulcerative colitis occurs most commonly during the first year of the disease, although it can occur at any time. While many patients respond to traditional therapy with intravenous steroids, further treatment with either intravenous cyclosporine or infliximab is often needed to suppress inflammation and avoid colectomy. These therapies are roughly equivalent in efficacy;4 the best one of these two drug treatments to use is that which the physician is most familiar and comfortable with. The physician and surgeon need to see the patient on a daily basis. The sick colitic is one of the best tests of a physician’s skill in patient care.

References


Surgical treatment of low rectal cancer: Current challenges and options

While total mesorectal excision is widely accepted as the preferred technique for low anterior resection of rectal cancer, the consequent low rectal anastomosis presents a significant risk of anastomotic leak, in particular when compared with alternative procedures such as abdominoperineal resection. The cause of leakage is often difficult to determine, although anatomical inaccessibility and less than optimal blood supply may be contributory factors.1 The risk of anastomotic leakage is evidently inversely associated with height of anastomoses and appears to be similar regardless of stapling technique. However, there appears to be an emerging trend towards reduced leakage in stapled low anastomosis. When oncologically feasible, double-stapled anastomosis is the preferred anastomotic technique.

“When oncologically feasible, double-stapled anastomosis is the preferred anastomotic technique”

Besides the stapled technique, reanastomosis after sphincter-preserving surgery can be performed with transabdominal handsaw or coloanal pull-through techniques. Technically, the traditional end-to-end, straight coloanal anastomosis (SCAA) is simpler, but it is associated with high rates of “anterior resection syndrome,” defined by increased rates of stool frequency, urgency and incontinence due to the loss of the rectal reservoir. To overcome these, alternative techniques, such as the colonic J-pouch, coloplasty and side-to-end anastomosis, have been developed. Functional outcomes (ie, stool frequency, faecal urgency, constipation) between these alternative techniques are generally similar, although colonic reservoirs (colonic J-pouch, coloplasty) have been found to be superior to SCAA in this aspect.2-4 Immediate postoperative complications are relatively similar between all restorative techniques.7

Against a setting of optimal surgery, the Dutch CKVO 95-04 trial confirmed the local control and survival benefit of preoperative radiation in patients with resectable rectal cancer, particularly those with stage II and III tumours. However, controversies remain regarding the role of postoperative radiation, patients who are most likely to benefit, and timing of surgery after preoperative radiation therapy, among others. From a practical viewpoint, preoperative radiation is not applicable to all rectal cancers. Postoperative radiation alone is less effective than preoperative radiation alone, and is thus not routinely recommended.7

References

Treatment of severe ulcerative colitis: Current treatment strategies

While intravenous corticosteroids are effective in most patients with severe ulcerative colitis (UC), approximately 30–40% of patients fail to respond.1-3 For these patients, an early decision must be made on whether to institute “rescue” medical therapy with cyclosporine or infliximab, or surgery. As such, an open discussion involving the patient, the gastroenterologist and the surgeon is paramount.

The relatively rapid response with cyclosporine makes its use attractive in the steroid-refractory setting.4 Despite high initial response rates, patients should be made aware that the risk of colectomy increases with cyclosporine treatment duration (20 to 69% at 1 and 5 years, respectively), and this risk appears to be higher in prior non-responders to thiopurine.5

Adverse effects associated with the use of cyclosporine remain a concern to physicians. Based on the observation from short-term studies, the adverse effects are mild, including vomiting, paraesthesia, tremor and hypertension. Long-term exposure to cyclosporine has been shown to cause nephrotoxicity and opportunistic infections.5 As such, prophylaxis against Pneumocystis jiroveci should be considered.

Among patients with severe steroid-refractory UC, a single infusion of infliximab was shown to be efficacious in preventing colectomy, with significantly less patients requiring colectomy compared with placebo at three months.7 In addition, the Active Ulcerative Colitis Trials 1 and 2 revealed higher rates of clinical remission and mucosal healing with infliximab maintenance therapy than with placebo.8 A pooled analysis of seven studies on anti-tumour necrosis factor-alpha agents further confirmed the benefits of infliximab in the treatment of moderate but not exclusively severe UC.9

Similar to cyclosporine, infliximab is not without its adverse effects, including serious and opportunistic infections, with rare cases of lymphoma or death.1 A French study did not find any significant difference in efficacy between cyclosporine and infliximab. Thus, the authors suggested that the selection of treatment should be based on physician experience.10 Sequential therapy with either cyclosporine following infliximab, or vice versa, is associated with potentially serious or fatal complications, and is generally not recommended.

When compared with medical therapy, surgery provides definitive treatment for severe UC. A surgical consult should always be obtained in patients failing primary therapy or being considered for infliximab or cyclosporine. Failure to respond to infliximab or cyclosporine within 5–7 days is associated with poor outcomes, and surgery is recommended in such a case (Figure).11 When surgery is indicated, total or subtotal colectomy with end ileostomy is the procedure of choice.11

References

Figure. A consensus algorithm for the management of severe UC. Adapted from reference 11

CXR, chest X-ray; AXR, abdominal X-ray; TB, tuberculosis
A number of parallels have been drawn between gut care and lawn care. In cases of altered gut microbiota composition due to antibiotic therapy or overgrowth of “weed-like” microbial species, strategies such as reseeding “good” microbes (probiotics) or introducing beneficial compounds (prebiotics) that promote its growth, can be employed. Alternatively, transplantation of the entire microbial system (faecal microbiota transplantation [FMT]) or narrow-spectrum antibiotics may be considered for select patients with aberrant gut microbiota.

Helicobacter pylori is a recognized “weed-like” gut bacterial carcinogen associated with abnormal DNA transcription, and gastric mucosal apoptosis and inflammation. Furthermore, dysbiosis of the gut microbiota has also been associated with diseases outside of the gastrointestinal (GI) tract, including obesity, diabetes and cardiovascular disease (Figure). Studies in both mice and humans have revealed that these metabolic disorders may result from a complex interplay between diet, host metabolism, the gut microbiota or their products, and the innate immune system.

FMT has not received mainstream attention until recent years, largely due to the global Clostridium difficile epidemic, and the renewed appreciation of the complexity of the gut microbiome and its impact on human health and disease.

Dutch researchers led by van Nood recently published the first randomized controlled trials of FMT for relapsing C. difficile infection. FMT was shown to be considerably superior to traditional antibiotic therapy, conferring a success rate of 81% following a single nasoduodenal infusion and 94% following a second infusion, while vancomycin 500 mg QID for 2 weeks with or without bowel lavage produced only 23-31% efficacy. The primary efficacy endpoint was the resolution of C. difficile-related diarrhoea without relapse after 10 weeks. In addition, comparative 16S rRNA gene-based analysis of faecal microbiota showed greater bacterial diversity after donor-faeces infusion. No significant differences in adverse events were noted other than mild infusion-related diarrhoea and abdominal discomfort.

Although robust data are not yet available for other GI diseases, a recent systematic review of 17 case series/reports found that FMT was associated with a reduction or complete resolution of symptoms in 76% of patients with inflammatory bowel disease (ie, ulcerative colitis and Crohn’s disease). Despite obvious limitations, this review has demonstrated empirically the potential role of FMT in the treatment of inflammatory bowel disease, at least when standard treatments have failed.

References

Figure. Non-GI diseases associated with gut microbiota dysbiosis. Adapted from reference 2
Non-alcoholic fatty liver disease: An update on management

The prevalence of non-alcoholic fatty liver disease (NAFLD) is strongly correlated with the prevalence of obesity. In addition, the prevalence of diabetes, metabolic syndrome and dyslipidemia was strikingly increased in patients with hepatic steatosis compared with normal controls. In Hong Kong, NAFLD affects 27% of the general population.

Identification of genetic and environmental modifiers of NAFLD contributes to better understanding of the pathogenesis and progression of the disease. The 1148M PNPLA3 polymorphism is present in 23–40% of the population and is associated with an increased risk of hepatic steatosis and inflammation. Lower serum levels of 25-hydroxyvitamin D are observed in NAFLD subjects compared with non-NAFLD subjects, implying a role for vitamin D as a modifiable environmental factor in the development of NAFLD.

Dietary modification is the first-line treatment for NAFLD subjects. In a study by Kirk and colleagues, caloric restriction with a low-fat or low-carbohydrate diet was associated with an equivalent reduction in hepatic steatosis content after 11 weeks, when subjects experienced 7% weight loss. Ryan and colleagues showed that the Mediterranean diet (a diet high in monounsaturated fatty acids), when compared with a low-fat-high carbohydrate diet, significantly reduced intrahepatic lipid (p=0.03) and improved insulin sensitivity (glucose infusion rate, p=0.03), even without weight loss in subjects with NAFLD (Figure). Furthermore, Estruch and colleagues reported that a Mediterranean diet supplemented with extra-virgin olive oil or nuts reduced the risk of major cardiovascular (CV) events among individuals at high CV risk.

Combined dietary weight-control approaches with physical exercise are now considered the most appropriate initial treatment of NAFLD. Weight loss has been shown to be positively correlated with resolution of NAFLD and improvement in liver histology. NAFLD patients who engaged in aerobic exercise were shown to have reduced hepatic fat, without concurrent changes in BMI or visceral fat mass. The use of pharmacological interventions, such as vitamin E and pioglitazone, has yielded promise in clinical studies for the treatment of NAFLD; however their long-term safety risks are not well understood and warrant further investigation.

References

Figure. Mediterranean diet was associated with improved intrahepatic lipid (A) and insulin sensitivity (B). Adapted from reference 11

MD, Mediterranean diet; LF/HCD, low fat-high carbohydrate diet; IHL, intrahepatic lipid; GINF, glucose infusion rate
10-day Sequential versus 10-day Bismuth-containing quadruple therapy as empirical first-line treatment for Helicobacter pylori: An open label randomized crossover trial (Summary of Gastroenterology and Hepatology Exit Dissertation June 2013)

Introduction
Helicobacter pylori (H. pylori) was first isolated in 1983 by Warren and Marshall.1 Since the discovery, many researches have been carried out to look at different aspects of this gram-negative microaerophilic bacterium. Its strong associations with recurrent peptic ulcer diseases were one of the first to be established and have greatly influenced the management of the peptic ulcer diseases thereafter. In addition, H. pylori is also an important risk factor for the development of gastric carcinoma and primary gastric mucosa-associated lymphoid tissue (MALT) lymphoma with H. pylori being classified as group 1 carcinogen by the World Health Organization International Agency for Research on Cancer.2 Effective treatment of this infective disease is therefore warranted.

Clarithromycin based triple therapy, consisted of a proton pump inhibitor (PPI), clarithromycin and amoxicillin, has been the standard first-line eradication regimen since its introduction in 1996.3 It is still regarded as the first line treatment option among experts across the world.4 However, the eradication rate is declining worldwide to an unacceptable ITT eradication rate of less than 80%. In some studies it was even less than 60%.5 The reduced effectiveness of H. pylori eradication is thought to be due to the rising clarithromycin resistance.6 The clarithromycin resistance rates published in 2011 to 2012 ranges between 5.2% in Belgium to 55.6% in Japan.7 Locally in Hong Kong, there appears to have an increasing trend in clarithromycin resistance rate being 4.7% in 1997 to 8.3% in 2001.8 It further rose to 13% in 2005.9

In response to the falling H. pylori eradication rate and the rising clarithromycin resistance, several new regimens including sequential therapy, concomitant therapy, hybrid therapy and levofloxacin-based therapy have been studied with variable success.10-12 The latest Maastricht IV Consensus Report suggests using bismuth containing quadruple therapy or sequential therapy as an alternative empirical first-line treatment, particularly in areas with high clarithromycin resistance.4

The aim of this study was to compare the eradication success rates of 10 day sequential therapy (SEQ) with a modified 10 day bismuth containing quadruple therapy (QUAD) as an empirical first line H. pylori in Hong Kong Chinese patients with a background of rising clarithromycin resistance. We further determined the role of these two regimens as empirical second line therapy in patients who failed the initial assigned regimen in a crossover design.

Patients and methods
Patients
This is a prospective, open-label, randomized study performed in the University Department of Medicine, Queen Mary Hospital, Hong Kong. Patients were identified in those referred to our department for the evaluation of dyspeptic symptoms and received upper gastrointestinal endoscopy for the first time between July 2011 and June 2012. Patients were eligible for recruitment if they were aged 18 years or older with documented H. pylori infection.

H. pylori infection was determined by either a positive rapid urease test or a positive identification of H. pylori in a histological sample using hematoxylin and eosin and/or Giemsa stain.

Patients were excluded if they had any of the followings: previous eradication therapy for H. pylori; known allergies to any of the study medications; recent use of antibiotics, bismuth preparation, probiotic preparation, proton pump inhibitors, non-steroidal anti-inflammatory drugs in the preceding 1 month; pregnant or lactating women; previous upper gastrointestinal surgery; alcohol or drug abuse or severe concurrent illness such as liver failure, renal failure and terminal malignancy.

The study protocol was approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster. All enrolled subjects provided written informed consent prior to the participation of the study. This trial is registered with ClinicalTrials.gov, number NCT 01760824.

Study design
Randomization sequences were generated by computer in blocks of four. All randomization codes were put in a sealed envelope containing pre-assigned treatment protocol. Each of the enrolled subjects was allocated to receive either 10 days of sequential (SEQ) therapy (esomeprazole 20 mg twice daily and amoxicillin 1 g twice daily for the first five days, followed by esomeprazole 20mg twice daily, clarithromycin 500mg twice daily and metronidazole 400mg four times daily for the subsequent 5 days) or 10 days of quadruple (QUAD) therapy (esomeprazole 20mg twice daily, bismuth subcitrate 120mg four times daily, tetracycline 500mg four times daily and metronidazole 400mg four times daily for a total of 10 days).

Written instructions were given to the patients to reinforce drug compliance. Compliance with treatment was evaluated by counting any unused study medications at the completion of treatment and non-compliance was defined as failure to take all of the study medications. All adverse events were recorded in a specific questionnaire by the research personnel. H. pylori eradication was determined by 13C-urea breath test (UBT) at 8 weeks after completion of the assigned eradication regimen.

Patients who failed the initial assigned eradication regimen as defined by a positive UBT at the end of 8 weeks were crossover to alternate treatment regimen. Again, drug compliance and adverse events were assessed as described above and a repeat UBT performed 8 weeks after the completion of the alternate regime.

The primary endpoint of the study was H. pylori eradication rates of first assigned - treatment by intention-to-treat and per-protocol analyses. The secondary endpoints were the H. pylori eradication rates in second-line treatment, frequency of adverse events and treatment compliance.

13C-Urea breath test
Patients were fasted for at least 6 hours before obtaining an initial breath sample. Each patient swallowed one Diabact™ (Orexo AB, Uppsala, Sweden) UBT tablet with 200mL of water. Each of the
Diabact tablet contained 50mg of $^{13}$C-urea and 456mg of anhydrous citric acid. A second breath sample was obtained 10 minutes later. All of the breath samples were analyzed by a purpose-built isotope ratio mass spectrometer in our hospital by a technician who was blinded to the treatment allocation. The cut-off value used was 2.5‰.13

**Statistical analysis**

Based on the previous meta-analysis studies,14, 15 we assumed the eradication rate of the SEQ group of 90% and QUAD group of 78%. The sample size estimation was 150 patients per arm with a power of 80% and a two-sided type 1 error of 5%, allowing 10% loss to follow-up.

Efficacy of *H. pylori* eradication rate was assessed by intention-to-treat (ITT) and per protocol (PP) analysis. Subjects who did not complete the assigned eradication regimen or did not return for UBT were excluded from the PP analysis. Categorical data comparisons were performed by Pearson’s chi-squared test or Fisher’s exact test, as appropriate. A two-sided P-value of less than 0.05 was considered significant. Statistical analysis was performed by using SPSS 20.0 software for Microsoft Windows (SPSS Inc., Chicago, Illinois).

**Results**

**Patient population**

A total of 357 patients were recruited into the study. There were 179 patients assigned to the SEQ therapy group with 41.9% male (n=75) and a mean age of 56.4±13.74. In the QUAD therapy group, there were 178 patients with 44.9% male (n=80) and a mean age of 56.4±13.93. The baseline demographic characteristics were similar in both groups (Table 1). A summary of the study is shown in figure 1. A total of 13 dropouts (7.3%) in the SEQ therapy group (six were lost to follow-up and seven were due to adverse effects of the medications). Similarly, there were 15 dropouts (8.4%) in the QUAD therapy group (four were lost to follow-up, one non-compliance to medication and 10 due to adverse effects of the medications).

![Figure 1: Trial profile](image)

**Figure 1** Trial profile

SEQ = Sequential therapy; QUAD = Quadruple therapy; UBT = Urea breath test; ITT = Intention-to-treat; PP = Per protocol
Gumurdulu Y, Serin E, Ozer B, et al. Low eradication rate of H. pylori therapy with low frequency of adverse events in Hong Kong.

In conclusion, both sequential therapy and bismuth-based quadruple therapy for primary treatment of H. pylori infection: systematic review and meta-analysis of 19 studies with a total of 24,303 patients showed a pooled eradication rate of 85.9% (95% CI: 83.4% - 88.3%).

**Table 1: Baseline characteristics of the study patients**

<table>
<thead>
<tr>
<th>Endoscopic diagnosis</th>
<th>SEQ therapy  (N = 179)</th>
<th>QUAD therapy (N = 178)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>75 (41.9%)</td>
<td>80 (44.9%)</td>
<td>NS</td>
</tr>
<tr>
<td>Mean age in years (SD)</td>
<td>56.4 (13.7%)</td>
<td>56.4 (13.9%)</td>
<td>NS</td>
</tr>
<tr>
<td>Smoker</td>
<td>14 (7.8%)</td>
<td>21 (11.8%)</td>
<td>NS</td>
</tr>
<tr>
<td>Alcohol drinkers</td>
<td>21 (11.7%)</td>
<td>25 (14.0%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Data are number of patients (%), unless otherwise stated
SEQ = Sequential therapy; QUAD = Quadruple therapy; NS = not significant

**Helicobacter pylori eradication rates**

The overall eradication rates by ITT and PP analysis is summarized in table 2. By PP analysis, the eradication rate of the SEQ group and QUAD groups were 95.2% (95% CI: 90.8 – 97.5%) and 98.8% (95% CI: 95.6 – 99.7%), respectively (Difference = -3.6%, 95% CI: -8% to 0.3%; P = 0.10). Based on the ITT analysis, the eradication rates were 89.4% (95% CI: 84 – 93.1%) in the SEQ group and 92.7% (95% CI: 87.9-95.7%) in the QUAD group (Difference = -3.3%, 95% CI: -9.5% to 2.8%; P = 0.36).

A total of 10 patients failed H. pylori eradication after completing the initial assigned treatment regimen - eight patients (4.8%) were from the SEQ group and two patients (1.2%) were from the QUAD group. The patients were then crossed over to receive the alternate treatment regimen. All ten of the patients had a negative UBT result eight weeks after the second course of treatment.

**Table 2: Helicobacter pylori eradication rates in the sequential therapy and quadruple therapy groups**

<table>
<thead>
<tr>
<th></th>
<th>SEQ therapy</th>
<th>QUAD therapy</th>
<th>P value</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intention-to-treat</td>
<td>89.4% (160/179)</td>
<td>92.7% (165/178)</td>
<td>0.36</td>
<td>-3.3%</td>
</tr>
<tr>
<td>95% CI (%)</td>
<td>84 -93.1</td>
<td>87.9 – 95.7</td>
<td></td>
<td>-9.5 – 2.8</td>
</tr>
<tr>
<td>Per protocol</td>
<td>95.2% (158/166)</td>
<td>98.8% (161/163)</td>
<td>0.10*</td>
<td>-3.6%</td>
</tr>
<tr>
<td>95% CI (%)</td>
<td>90.8 -97.5</td>
<td>95.6 – 99.7</td>
<td></td>
<td>-8.0 – 0.3</td>
</tr>
</tbody>
</table>

Data are presented in % (n/N), unless otherwise stated
SEQ = Sequential therapy; QUAD = Quadruple therapy; CI = Confidence interval
*Fisher’s Exact test statistics used
Adverse events and compliance
The overall adverse events were significantly higher in the QUAD group (16.7%) than in the SEQ group (8.1%; \( P = 0.032 \)). The most common adverse events reported in the QUAD group were nausea (3.4%), vomiting (2.3%) and skin rash (2.3%). In the SEQ group, skin rash (2.3%) and taste disturbance (1.7%) were the most commonly reported adverse events. All the reported side effects were mild and resolved rapidly after the end of treatments. The dropout rates for the SEQ group and the QUAD group were 13 (7.3%) and 15 (8.4%), respectively (\( P = 0.699 \)). Table 3 summarizes the frequencies of adverse events for the two treatment groups.

Table 3: Adverse events of the study patients

<table>
<thead>
<tr>
<th></th>
<th>SEQ therapy (N = 179)</th>
<th>QUAD therapy (N = 178)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>1 (0.6%)</td>
<td>6 (3.4%)</td>
<td>0.067</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2 (1.2%)</td>
<td>4 (2.3%)</td>
<td>0.448</td>
</tr>
<tr>
<td>Increased stool frequency</td>
<td>1 (0.6%)</td>
<td>3 (1.7%)</td>
<td>0.248</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>1 (0.6%)</td>
<td>3 (1.7%)</td>
<td>0.371</td>
</tr>
<tr>
<td>Skin rash</td>
<td>4 (2.3%)</td>
<td>4 (2.3%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Taste disturbance</td>
<td>3 (1.7%)</td>
<td>2 (1.1%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1 (0.6%)</td>
<td>3 (1.7%)</td>
<td>0.371</td>
</tr>
<tr>
<td>Headache</td>
<td>1 (0.6%)</td>
<td>2 (1.1%)</td>
<td>0.623</td>
</tr>
<tr>
<td>Insomnia</td>
<td>0 (0%)</td>
<td>1 (0.6%)</td>
<td>0.499</td>
</tr>
<tr>
<td>Fatigue</td>
<td>0 (0%)</td>
<td>1 (0.6%)</td>
<td>1.0</td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td><strong>14 (8.1%)</strong></td>
<td><strong>29 (16.7%)</strong></td>
<td><strong>0.032</strong></td>
</tr>
</tbody>
</table>

Recent data on the effectiveness of bismuth-based quadruple therapy was pooled in a meta-analysis that included nine randomized controlled studies from 2003 to 2008, carried out mainly in the Western countries.\(^{13}\) The overall pooled ITT eradication rate was 78.3%. In contrast, our study showed that bismuth-based quadruple therapy was extremely effective with an ITT eradication rate of 95.2%. The reason for the marked discrepancy was not apparent. The differences in the duration of treatment should not have a high impact as seen in the meta-analysis by Luther et al.\(^{15}\) The eradication rates were similar with 80.1% and 78.9% in seven and ten days of treatment, respectively. Another known factor that may affect the eradication rate is the presence of metronidazole resistance. It was shown that the efficacy of quadruple therapy reduced by 14% in the presence of metronidazole resistance.\(^{20}\) Although no formal antimicrobial resistance was measured in this study, the reported metronidazole resistance in Hong Kong was 58.3% in 2001 and 86% in 2005.\(^{7}\) If we assume the metronidazole resistance remained stable since 2005, then its effect on the bismuth-based quadruple therapy was definitely lower than previously thought.

Despite the complexity of the treatment regimen and the large number of tablets to be taken, only one patient in the quadruple therapy group failed to complete all the prescribed medications. This high level of compliance rate was also seen in the meta-analysis.\(^{15,21}\) With the availability of new single (three-in-one) capsule containing bismuth subcitrate, metronidazole and tetracycline;\(^{24}\) the number of tablets needs to be taken in the quadruple group will be substantially decreased and will likely increase in the drug compliance. The overall adverse events were mild and infrequent, and were similar in both treatment arms.

The effectiveness of these regimens as second-line therapy seemed to be excellent albeit tested on only ten patients who failed the initial therapy. All of the patients had H. pylori eradicated after completed the crossover regimen. This combination approach might be beneficial as the key antibiotics involved in the two regimens were very different and possibly able to cover the resistance strains emerged from the initial therapy. However, further trials were needed to assess the efficacy of this cross-over approach.

Our study has several limitations. Firstly, antimicrobial resistance was not tested as the study was performed under clinical practice conditions and H. pylori antimicrobial resistance is not routinely done for first-line therapy. Secondly, as the present study was set up as a superiority trial, we cannot draw any conclusions whether one treatment is equivalent or non-inferior to the other treatment based on the statistically non-significant result. It is arguable that our current sample size was insufficient to demonstrate a statistical significant difference between the two study groups. Based on the current results, we need a sample size of at least 350 per arm to give us a power of 80% and a two-sided type I error of 5% in a superiority trial or a sample size of 1820 per arm with a superiority margin of 5% in a non-inferiority trial. However, given the excellent eradication rates of both treatment arms (>95% according to PP analysis), the demonstration of a statistically significant difference will be unlikely to confer any additional benefits in clinical practice and therefore may

Discussion
This is the first trial to date comparing 10-day sequential therapy with 10-day bismuth-based quadruple therapy as first line H. pylori eradication. Our results showed that both eradication regimen were highly effective in eradicating H. pylori as represented by >95% eradication rate by PP analysis (and >90% by ITT analysis), thus achieving a grade A standard in the report card system.\(^{16}\) The remarkable eradication rate in sequential therapy was comparable to the results published by the Italian researchers with a mean ITT eradication rate of 92.4%.\(^{14}\) On the other hand, the reported results of the sequential therapy from the Asian countries were variable, ranged from 81.9% in Korea,\(^{17}\) 82.6% in China\(^{18}\) to 90.5% in Taiwan.\(^{19}\) In Hong Kong, this is the first ever reported data on the eradication rate of the sequential therapy.
not be clinically relevant. Thirdly, due to the small number of patients with failed primary eradication therapy may be warranted.

In conclusion, both sequential therapy and bismuth-based quadruple therapy were highly effective in eradicating *H. pylori* as a first-line therapy with low frequency of adverse events in Hong Kong.

**Acknowledgements**

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**References**

12. Hsu PI, Wu DC, Wu JY, Graham DY. Modified sequential *Helicobacter pylori* therapy: proton pump inhibitor and amoxicillin for 14 days with clarithromycin and metronidazole added as a quadruple (hybrid) therapy for the final 7 days. *Helicobacter* 2011;16:139-45.
5. Gumurdulu Y, Serin E, Ozer B, et al. Low eradication rate of eradication therapy may be warranted.

3. Unge P. Review of assessments of second line therapy was under powered. Further H. pylori eradication with a 20. Fischbach L, Evans EL. Meta-analysis: the effect of antibiotic resistance status on

14. Gatta L, Vakil N, Leandro G, Di Mario F, Vaira D. Sequential therapy or triple


Our results showed that both eradication regimen were 10-day bismuth-based quadruple therapy as first line sequential therapy.

Dr. Jodis T.W. Lam welcomed the delegates and thanked the co-organizing societies and sponsors for their support and contributions to the 16th Joint Annual Scientific Meeting.

There were 8 lectures covering hot topics in gastroenterology, hepatology and endoscopy delivered by renowned speakers.

The Meeting was attended by 256 healthcare professionals. Panel discussions were actively participated. Souvenirs were presented to the speakers and sponsors in appreciation of their contributions.

### Topics

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Presentation of Honorary Fellowship by President, Dr. Wai-Cheung Lao

Case Discussion: ERCP

Annual General Meeting

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